Journal of Cardiology 63 (2014) 53–59

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

Polyunsaturated fatty acids for the prevention of atrial fibrillation after cardiac surgery: An updated meta-analysis of randomized controlled trials

Baowei Zhang (Msc)[1], Ya Zhen (MSc)[1], Aibin Tao (MSc), Zhonghua Bao (BS), Guohui Zhang (MD, PhD)*

Department of Cardiology, The Affiliated People's Hospital of Jiangsu University, Zhenjiang, Jiangsu, China

ARTICLE INFO

Article history:
Received 18 February 2013
Received in revised form 20 April 2013
Accepted 19 June 2013
Available online 1 August 2013

Keywords:
Polyunsaturated fatty acids
Cardiac surgery
Atrial fibrillation
Meta-analysis

ABSTRACT

Background: Several clinical trials showed inconsistent results of the effect of polyunsaturated fatty acids (PUFA) on the incidence of post-operative atrial fibrillation (POAF). The aim of this meta-analysis is to investigate the effect of PUFA on the incidence of POAF in patients undergoing cardiac surgery.
Methods and results: PUBMED, EMBASE, Cochrane Library, and Google Scholar databases were searched for randomized controlled trials. Statistical heterogeneity was assessed using I^2 statistic and Cochran's Q statistic. The effect of PUFA on the incidence of POAF was presented as risk ratio (RR) with 95% confidence intervals (CIs) using a fixed effect model or random effect model depending on statistical heterogeneity. Subgroup analyses were conducted based on the baseline characteristics of patients, types of surgery, the ratio of eicosapentaenoic acid (EPA)/docosahexaenoic acid (DHA), and the quality of the studies. Eight trials with 2687 patients were included in the analysis. Treatment with PUFA had no effect on the incidence of POAF in patients undergoing cardiac surgery compared to placebo [RR 0.86; 95% CI 0.71–1.04, $p = 0.110$]. Subgroup analyses showed the quality of the studies, the ratio of EPA/DHA, accompanied with diabetes might impact the effect of PUFA on POAF. No evidence of publication bias was detected.
Conclusions: The present analysis suggests that treatment with PUFA preoperatively has no effect on the incidence of POAF in patients undergoing open heart surgery. However, patients with diabetes might get benefits from the treatment with PUFA preoperatively.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia after cardiac surgery. Despite ongoing efforts to prevent the occurrence, the incidence of post-operative atrial fibrillation (POAF) ranges from 20% to 70% [1]. In addition, POAF is associated with prolonged hospitalization, and increased costs, morbidity, and mortality [2]. Furthermore, classic anti-arrhythmic drugs have not been effective in preventing POAF [3]. Therefore, we should try our best to investigate new strategies to prevent the occurrence of POAF in patients undergoing open heart surgery.

Intake of fish or fish oil appears to reduce risk of coronary death, perhaps through reduction of primary ventricular arrhythmias [4]. Animal experiments showed that polyunsaturated fatty acids (PUFA) suppressed congestive heart failure-induced atrial structural remodeling and AF promotion [5]. A clinical trial also showed beneficial effect of PUFA on prevention of POAF in patients undergoing coronary artery bypass grafting (CABG) [6]. However, some other trials of PUFA reported conflicting results on its efficacy in preventing POAF [7–13]. Since earlier meta-analyses estimating the effect of PUFA on POAF in patients undergoing cardiac surgery [14], the results of four new trials have been reported. These studies increased almost five times the number of patients enrolled in randomized trials. So we performed a new meta-analysis of randomized controlled trials to estimate the effect of PUFA on preventing POAF in patients undergoing cardiac surgery.

Materials and methods

Literature search

A literature search was performed on the PUBMED, EMBASE, Cochrane Library, and Google Scholar databases to identify all the studies that reported the effect of PUFA on the prevention of POAF

* Corresponding author at: Department of Cardiology, The Affiliated People's Hospital of Jiangsu University, 8 Dianli Road, Zhenjiang, Jiangsu 212002, China. Tel.: +86 551 88915298; fax: +86 551 88915298.
E-mail addresses: zhangbaowei3@126.com (B. Zhang), zhangguohui2013@yahoo.com.cn (G. Zhang).
[1] Co-first author.

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http://dx.doi.org/10.1016/j.jjcc.2013.06.014

in patients undergoing cardiac surgery. The following medical subject headings were used: cardiac surgery, atrial fibrillation, and polyunsaturated fatty acids (or fish oil). Searches were also performed under the headings of coronary artery bypass graft, cardiothoracic surgery, and polyunsaturated fatty acids. For all relevant publications, the records retrieved with the "related articles" link in PUBMED were reviewed; reference lists were checked for other relevant studies. The final literature search was finished on December 31st, 2012 and all the searches were limited to English language publications. The major inclusion criteria were: (1) the design was a randomized controlled clinical trial; (2) the patients in the trial underwent cardiac surgery; (3) the main outcomes included the incidence of POAF. The major reasons for exclusion of studies were: (1) overlapping data; (2) patients aged < 18 years old; (3) history of AF or Class I/III anti-arrhythmic medications; and (4) data published in the form of abstracts without peer-reviewed publication of manuscripts.

Data collection and quality assessment

Two investigators (B. Zhang and Y. Zhen) independently reviewed all potentially eligible studies using predefined eligibility criteria and collected data from the included trials. Any discrepancy was resolved by consensus. Baseline characteristics of patients were extracted as well as data about each trial's intervention and outcomes assessed. Quality assessments were evaluated with Jadad quality scale, which enables the adequacy of randomization, blinding, and the handling of withdrawals and dropouts, and a numerical score between 0 and 5 was assigned as a measure of study design [15].

Statistical analyses

Statistical analyses were performed using STATA 11.0 (StataCorp LP, College Station, TX, USA) utilizing the METAN and METBIAS modules [16]. The effect of PUFA on the incidence of POAF was presented as risk ratio (RR) with 95% confidence intervals (CIs). Heterogeneity was evaluated with Cochran's Q statistic and quality by I^2 statistic. A value of $p < 0.1$ for Q test or $I^2 > 50\%$ indicated significant between-study heterogeneity. If no heterogeneity was present, fixed effect meta-analysis was performed to calculate RR. Alternatively, random effect meta-analysis was performed when heterogeneity existed. Publication bias was evaluated by Begg's and Egger's method. Results were considered statistically significant if $p < 0.05$. Sensitivity analyses were undertaken by omitting one study at a time to examine influence of one study on the overall summary estimate, and fixed or random effect models described above were used.

We explored possible explanations for heterogeneity according to a prior hypothesis, which included differences in the baseline characteristics of patients, concurrent medications that might influence the incidence of AF, types of cardiac surgery, the ratio of eicosapentaenoic acid (EPA)/docosahexaenoic acid (DHA), and the quality of studies. Specifically, we compared the results of studies grouped by the following factors: (1) mean age; (2) male proportion; (3) mean left ventricular ejection fraction (≥55% vs <55%); (4) proportion of patients using beta-blockers, angiotensin-converting enzyme inhibitors, and statins; (5) types of cardiac surgery (CABG only vs CABG and valve surgery); (6) concomitant diseases, such as diabetes and hypertension; (7) EPA/DHA ratio in the PUFA; and (8) Jadad score (>3 vs ≤3). Recognizing that any cut point is to some extent arbitrary, we chose cut points before analyzing the data using 2 criteria. First, thresholds had to be biologically sensitive; and second, they had to divide the trials into 2 subgroups with a more or less similar number of trials.

Results

Search results

Our preliminary search yielded 87 potential literature citations. After the evaluation, a total of 79 articles were excluded for different reasons. Eight trials with 2687 patients (1337 patients assigned to PUFA group and 1350 patients assigned to the control arm) were included in the analysis. Of the 8 studies, 5 [7,8,10,12,13] reported that there was no effect of PUFA on POAF after cardiac surgery, and another 3 studies [6,9,11] showed that treatment with PUFA preoperatively could reduce the incidence of POAF significantly. The characteristics of included studies are shown in Table 1.

Baseline characteristics of patients and quality of the included studies

The baseline characteristics of patients enrolled are summarized in Table 2. There was no significant difference in the baseline characteristics of patients between the two groups. The mean age of patients in individual trials ranged from 63.4 to 68 years. The proportion of males was 75.9% and 74.2% in the PUFA and control groups, respectively. Diabetes was present in 28.1% and 28.4% of patients in the PUFA and control groups, respectively. Hypertension was present in 75.2% and 72.4% of patients in the PUFA and control groups, respectively. We used the Jadad quality scale to evaluate the quality of the included studies. There were 5 studies with Jadad scores more than 3, and another 3 studies in our analysis had Jadad scores less than or equal to 3 (Table 3).

Effect of PUFA on the incidence of post-operative atrial fibrillation

Fig. 1 shows a forest plot comparing the incidence of POAF in patients treated with PUFA to those who did not receive PUFA. I^2 statistic and Q test showed that there was a significant heterogeneity of treatment effect among the studies for POAF ($I^2 = 53.6\%$, $\chi^2 = 15.8$, $p = 0.035$), so the random effect model was used to pool the data. Treatment with PUFA had no effect on the incidence of POAF in patients undergoing cardiac surgery compared to placebo [RR 0.856; 95% CI 0.707–1.036, $p = 0.110$; Fig. 1].

Sensitivity analyses

First, sensitivity analyses were performed by omitting one study at a time and calculating the pooled RR for the remaining studies. This procedure was used to ensure that no individual study was entirely responsible for the combined results. Second, the pooled RR was estimated using fixed effect model and random effect model, respectively. Sensitivity analysis indicated that the results of the meta-analysis were reliable and stable.

Subgroup analyses

Subgroup analyses were separately performed to investigate heterogeneity. The results showed that concomitant diabetes, the ratio of EPA/DHA in the PUFA, and the quality of the study might impact the effect of PUFA on AF after open heart surgery (Table 4).

Risk of publication bias

Funnel plots were constructed to assess the risk of publication bias. The Egger's and Begg's tests showed no potential publication bias existed among the included trials (Egger's test: $p = 0.298$; Begg's test: $p = 0.174$; Fig. 2).

Table 1
Characteristics and quality of enrolled studies.

Study	No. of patients	Include criteria	Exclude criteria	Treatment group	Control group	POAF diagnosis criteria
Calo (2005)	160	Age >18 years; sinus rhythm and stable hemodynamic conditions	Valvular surgery; history of SVA or Class I/III antiarrhythmic medications	Two capsules/day PUFA five days before surgery and continued until discharge	Usual care	Duration >5 min or requiring intervention
Farquharson (2011)	194	Age >18 years; CABG and/or valve repair or replacement	History of AF/af or Class I/III antiarrhythmic medications; urgent surgery; heart failure(NYHA4); MI within2 weeks	15 ml/day fish oil for 3 weeks before surgery and continued 6 days after surgery or until discharge	Sunflower oil	Duration ≥10 min or requiring intervention
Heidarsdottir (2010)	168	Scheduled for elective or urgent open heart surgery; age≥40years	History of SVA or Class I/III anti-arrhythmic medications; emergent operation	PUFA initiated 5–7 days before surgery and continued to discharge but no longer than 2weeks after the surgery	2 g/d olive oil	Duration >5 min
Heidt (2009)	102	Age >18 years; sinus rhythm and stable hemodynamic conditions; freedom from angina	Concomitant valve surgery; history of SVA or anti-arrhythmic therapy	100 mg/kg/d	100 mg/kg/d soya oil	Duration >15 min
Mozaffarian (2012)	1516	Age >18 years; scheduled for cardiac surgery; sinus rhythm	Absence of sinus rhythm; regular use of fish oil; known allergy or intolerance to fish oil or olive oil; pregnant; existing or planned cardiac transplant or use of ventricular assist device	10-g preoperative loading dose over 5 days followed by 2 g/d postoperatively	Olive oil	Arrhythmias of at least 30 s duration
Sandesara (2012)	243	18–85 years old; undergoing elective CABG with or without concomitant valve surgery	Emergency CABG; unstable angina; heart failure; persistent AF or AF at the time of screening; planned surgery of AF; usage of Class I/III antiarrythmic drug; patients with PM or ICD; pregnancy; usage of PUFA at the time of screening	4 g/d PUFA before surgery and 2 g/d after surgery until the primary end point or 14days	A matching corn oil placebo	Any episode of AF or flutter requiring intervention
Saravanan (2010)	103	Age >18 years; undergo elective CABG	History of AF or Class I/III antiarrythmic drug	2 g/d n-3 PUFA	2 g/d olive oil	Duration >30 s
Sorice (2011)	201	Age >18 years; sinus rhythm and stable hemodynamic conditions	History of AF or Class I/III antiarrythmic drug; severe valvular disease	850–882 mg PUFA initiated 5–7 days before surgery and continued to discharge	NA	Duration >5 min or requiring intervention

POAF, post-operative atrial fibrillation; CABG, coronary artery bypass grafting; AF, atril fibrillation; PM, pacemaker; ICD, implantable cardioverter defibrillator; SVA, supraventricular arrhythmias; MI, myocardial infarction; NYHA, New York heart association; PUFA, polyunsaturated fatty acids; NA, not available.

Discussion

AF is the most common complication encountered after cardiac surgery. The incidence of POAF has increased continuously over the past decades with the aging of the population undergoing cardiac surgery. The underlying mechanisms involved in the development of POAF are multifactorial and are for the moment far from being fully elucidated. But there is an increasing body of evidence that inflammation and oxidative stress play important roles in the pathogenesis of POAF [17]. Resolvin and protectin, bioactive mediators in the process of the metabolism of PUFA in the cells, showed anti-inflammatory effects and prompted the resolution of inflammation [18]. A meta-analysis found that dietary PUFA was associated with plasma inflammatory biomarker levels, reflecting lower level of inflammation in cardiovascular diseases [19]. Some experiments and trials also showed the antioxidant effect of PUFA [20,21]. In addition, PUFA had an antiarrhythmic effect through direct steric interference with sodium, potassium, and calcium channels in the cardiac myocyte membrane [22]. Therefore, PUFA may have an effect on preventing POAF in patients undergoing cardiac surgery.

Table 2
Baseline characteristics of patients in trials enrolled.

Study	Age (years)		Male (%)		Diabetes (%)		HTN (%)		COPD (%)		LVEF (%)		LAD (mm)	
	PUFA	Control	PUFA	Control	PUFA	Control	PUFA	Control	PUFA	Control	PUFA	Control	PUFA	Control
Calo (2005)	66 ± 8	65 ± 9	86	84	32.9	32.1	78.5	81.5	16.4	16	56 ± 12	55 ± 11	40 ± 5	40 ± 5
Farquharson (2011)	64 ± 11	64 ± 10	82	64	27	36	78	77	9	12	65 ± 13	64 ± 13	NA	NA
Heidarsdottir (2010)	67(45–82)	67(43–82)	81.9	76.9	15.7	15.3	61.4	64.7	78.3	74.1	60(15–70)	60(15–77)	NA	NA
Heidt (2009)	68 ± 10	65 ± 14	73	64	NA	NA	NA	NA	NA	NA	52 ± 15	52 ± 16	40 ± 5	41 ± 5
Mozaffarian (2012)	63.8 ± 12.6	63.6 ± 12.4	72.7	71.6	25.7	26.3	76.2	74.9	10.6	11.9	56.6 ± 11.4	56.8 ± 11.3	42.1 ± 7.8	42.2 ± 7.6
Sandesara (2012)	63.4 ± 9.5	62.0 ± 11.4	78	83	38	35	89	88	18	11	52.0 ± 11.4	53.4 ± 13.5	38 ± 8	40 ± 8
Saravanan (2010)	64(58–71)	68(64–73)	77	82	13	16	35	29	8	10	10%≤55%	8%≤55%	4%≥2.3 cm/m²	6%≥2.3 cm/m²
Sorice (2011)	63 ± 13	63 ± 9	79	84	42	43	72	57	28	38	52 ± 10	53 ± 7	41 ± 9	40 ± 5

Data are presented as the mean value ± SD or number (%) of patients. PUFA, polyunsaturated fatty acids; HTN, hypertension; COPD, chronic obstructive pulmonary disease; LEVF, left ventricular ejection fraction; LAD, left atrium diameter; NA, not available.

The previous meta-analyses showed that administration with PUFA preoperatively had no effect on the incidence of POAF in patients undergoing open heart surgery [14,23,24]. But there were fewer RCTs enrolled in the meta-analyses. Since then, the results of 4 RCTs with a large number of patients have been published. We performed this meta-analysis of 8 RCTs with 2687 patients to evaluate the effect of PUFA on the incidence of AF in patients undergoing cardiac surgery. Our result showed that treatment with PUFA preoperatively failed to reduce the incidence of POAF.

Considering the significant heterogeneity existing in this pooled analysis, we performed subgroup analyses to better understand the association in different subgroups. The results indicated that patients with diabetes appeared to be likely to get benefits from PUFA therapy preoperatively. However, several factors might influence the potential benefits of PUFA supplementation on POAF.

First, patients from different areas may have different responses to the supplementation with PUFA. The diet in Iceland is mainly composed of seal and whale which is extremely rich in marine PUFA. So the people from Iceland, including patients enrolled by Heidarsdottir et al. [8], might have a higher baseline level of serum PUFA. Some experiments showed there was a low threshold for the incorporation of PUFA into the cell membrane [25]. Therefore, the daily diet may have resulted in the patients from Iceland having a higher baseline level of PUFA, which passed the threshold for the incorporation of PUFA into the cell membrane. This could explain the result that there was no effect of the administration with PUFA in patients enrolled by Heidarsdottir et al. [8].

In addition, different types of surgery and difference between surgical procedures would also influence the incidence of POAF and the effect of PUFA treatment. For example, there were some approaches for mitral valve surgery and some differing incisions on the atrium. The design of atrial incision may be related to the incidence of POAF. A multicenter Vererans Affairs study found that the surgery type would influence the incidence of POAF and the patients undergoing valve surgery had a higher rate of POAF than the patients with CABG [26]. In the study by Sorice et al. [11], the researchers found that administration of PUFA significantly reduced the incidence of POAF in patients undergoing "on-pump" CABG surgery. However, PUFA had no effect in the patients with "off-pump" surgery. In the study by Farquharson et al., the researchers found a trend toward a greater decrease in AF with PUFA in patients undergoing valve surgery compared to those with CABG only [7]. In our subgroup analyses, we failed to demonstrate that different types of surgery would influence the effect of PUFA on the incidence of POAF. However, we just divided the trials into CABG-only group and CABG + valve surgery group. The proportion of valve surgery and the components of the CABG were not considered.

Among the trials included in this meta-analysis, there was a significant difference in the diagnostic criteria of POAF. In the trial by Saravanan et al. [10], the diagnostic criterion of POAF was an episode of AF > 30 s. In the trial by Heidt et al. [9], the criterion was an episode of AF for longer than 15 min. In the study by Farquharson et al. [7], the diagnostic criterion of POAF was episode of AF duration ≥10 min or requiring intervention. So the different diagnostic criteria of POAF would change the rate of POAF and influence the potential benefits of administration with PUFA in patients undergoing cardiac surgery.

The favorable effect of PUFA on POAF was originally attributed to EPA. However, there is more DHA than EPA accumulated in the body and DHA has broadly similar biologic effects. Some trials suggested that there were some differential properties between EPA and DHA [27]. Some experiments showed that DHA, at lower concentration than EPA, could block the ion channels in the myocyte, some of

Table 3
Jadad score of the trials enrolled in this meta-analysis.

Study	Randomization	Double blinding	Withdrawals and dropouts	Jadad score
Calo (2005)	The method of randomization was based on computer-generated randomization list	No-blind	A description of withdrawals and dropouts	3
Farquharson (2011)	The method of randomization was based on computer-generated randomization list using blocks of 20	The method of double blinding was described and it was appropriate	A description of withdrawals and dropouts	5
Heidarsdottir (2010)	The study was described as randomized	The method of double blinding was described and it was appropriate	A description of withdrawals and dropouts	4
Heidt (2009)	The study was described as randomized	The method of double blinding was described and it was appropriate	Not describe the follow-up	3
Mozaffarian (2012)	The method of randomization was by means of computer-generated numbers	The method of double blinding was described and it was appropriate	A description of withdrawals and dropouts	5
Sandesara (2012)	The study was described as randomized	The method of double blinding was described and it was appropriate	A description of withdrawals and dropouts	4
Saravanan (2010)	Random assignment was based on a computer-generated randomization list obtained using blocks of size 4	The method of double blinding was described and it was appropriate	A description of withdrawals and dropouts	5
Sorice (2011)	The study was described as randomized	No-blind	A description of withdrawals and dropouts	2

which were present only in atrial cells [28]. The ratios of EPA and DHA were different among the trials enrolled in our meta-analysis. EPA/DHA in the trial by Calo et al. was 1/2 [6], but the ratio was 1.2/1 in the trial by Saravanan et al. [10]. Our results of subgroup analyses showed that the ratio of EPA/DHA < 1 in the PUFA might have a good effect on the incidence of AF after cardiac surgery. However, the quality of trials in the group of EPA/DHA < 1 was lower than in the group of EPA/DHA > 1. The subgroup analyses also indicated that the quality of the trials would influence the results of the meta-analysis.

The present meta-analysis has several features that distinguish it from the similar meta-analyses that were published. First, we included 4 additional randomized controlled trials, and the number of patients in our meta-analysis is far larger than that in the previous meta-analyses. Second, our meta-analysis showed that patients with diabetes might get benefits from treatment with PUFA preoperatively. A retrospective cohort study found that patients with diabetes had worse prognosis than patients without diabetes who underwent cardiac surgery [29]. Therefore, this result may be important for patients in this sub-group.

Study limitations

There are limitations of the present study. Lack of patient-specific data and the inclusion of trials of varying quality and design are limitations common to all meta-analyses. However, to at least partly nullify the latter factors, we included only randomized controlled trials. In addition, the appropriate dose of PUFA and the appropriate ratio of EPA and DHA remain uncertain. Further, the diagnostic criterion of POAF was arbitrary in the studies included in this analysis. However, the definition of AF episodes was shown in the 2012 Heart Rhythm Society/European Heart Rhythm Association/European Cardiac Arrhythmia Society Expert Consensus Statement on catheter and surgical ablation of AF. In this statement,

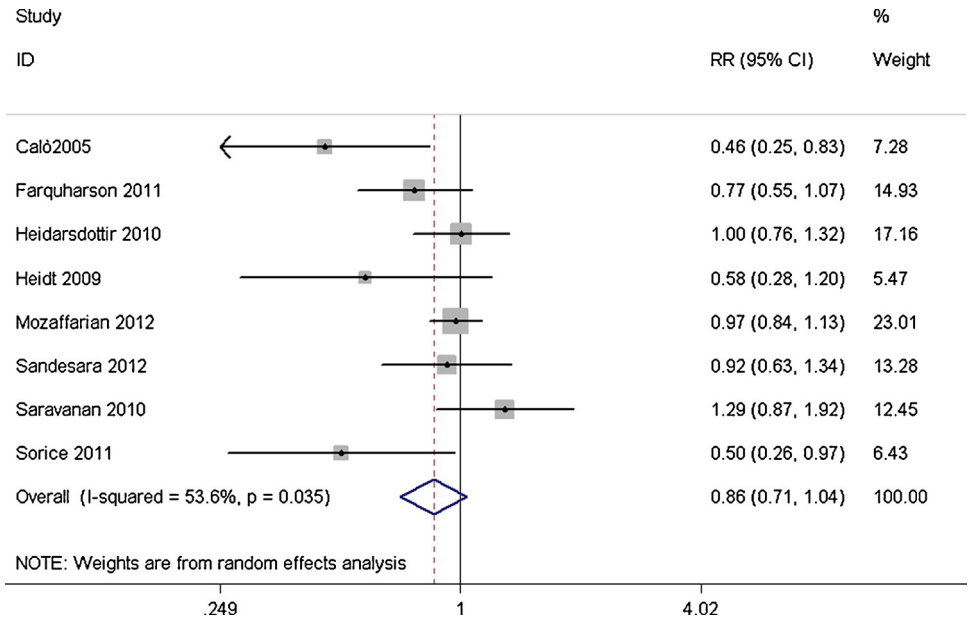

Fig. 1. Forest plot of risk ratio (RR) for treatment with polyunsaturated fatty acids on the incidence of atrial fibrillation after cardiac surgery. CI, confidence interval.

Table 4
Results of sub-group analyses.

Subgroup	Studies (*N*)	RR (95% CI)	*p*-Value
Age (years)			
≤65	4	0.86(0.70–1.06)	0.149
>65	4	0.82(0.53–1.27)	0.377
Male proportion			
≤80%	4	0.921(0.793–1.068)	0.275
>80%	4	0.762(0.473–1.229)	0.265
LVEF			
≤55%	3	0.704(0.468–1.058)	0.092
>55%	5	0.911(0.732–1.133)	0.400
Type of surgery			
CABG only	4	0.666(0.369–1.202)	0.177
CABG+ valve	4	0.945(0.840–1.063)	0.342
Therapy with statin			
≤70%	3	0.647(0.364–1.1.49)	0.137
>70%	3	0.955(0.709–1.286)	0.763
Therapy with β-blocker			
≤70%	4	0.713(0.507–1.004)	0.053
>70%	3	1.041(0.857–1.265)	0.683
Therapy with ACEI			
≤70%	4	0.859(0.699–1.056)	0.149
>70%	3	0.787(0.274–2.255)	0.655
Jadad score			
≤3	3	0.502(0.343–0.734)	<0.001
>3	5	0.969(0.863–1.088)	0.590
Diabetes			
≤30%	3	1.099(0.888–1.145)	0.895
>30%	4	0.693(0.511–0.939)	0.018
Hypertension			
≤70%	3	0.935(0.612–1.429)	0.757
>70%	4	0.825(0.646–1.055)	0.125
EPA/DHA			
≤1	2	0.476(0.305–0.743)	0.001
>1	5	0.969(0.863–1.088)	0.590

RR, risk ratio; CI, confidence intervals; LVEF, left ventricular ejection fraction; CABG, coronary artery bypass grafting; ACEI, angiotensin converting enzyme inhibitor; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.

any arrhythmia that had the electrocardiographic (ECG) characteristics of AF and lasted sufficiently long for a 12-lead ECG to be recorded, or at least 30 s on a rhythm strip, should be considered an AF episode [30]. Further study with this new definition of AF episodes, and the optimal dose and composition of PUFA is needed to identify the effect of PUFA on POAF.

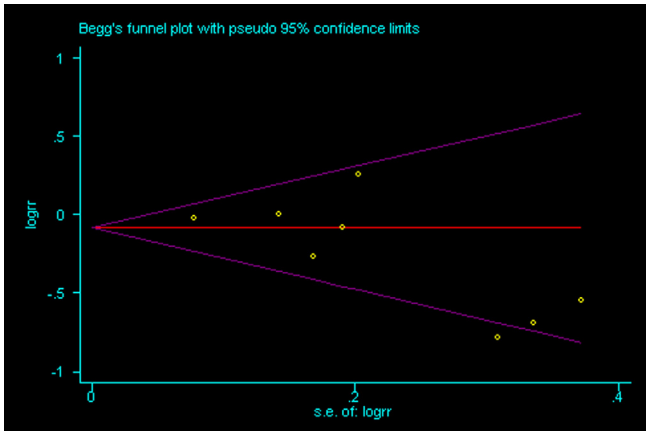

Fig. 2. Begg's funnel plot with pseudo 95% confidence intervals to assess for evidence of publication bias.

Conclusion

The present analysis suggests that treatment with PUFA preoperatively had no effect on the incidence of POAF in patients undergoing open heart surgery. However, patients with diabetes might benefit from treatment with PUFA preoperatively.

Disclosure

There are no conflicts of interests to disclose.

Acknowledgement

We thank Professor Heidt for the free full text of his article.

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